The Clinical Trial Model Is Up for Review

Time, Expense, and Quality of Results Are at Issue, As Is the Relationship to Drug Pricing

Stephen Barlas

The storm seeded by the pricing of Sovaldi has led payers, patients, and the federal government to seek cover from what some view as problematic pharmaceutical industry practices, including a few partly outside of the industry's control.

Sovaldi's $84,000 list price for a course of treatment has raised questions about how a company such as Gilead Sciences, Inc., decides on a price tag. The answer may hinge—in small or large part, depending on who's talking—on the length and complexity of the clinical trials a company must conduct in order to win approval from the Food and Drug Administration (FDA) for the new drug. Sundeep Khosla, MD, Dean for Clinical and Translational Science at the Mayo Clinic, says clinical trials are subject to the "Valley of Death." He explains, "This refers to the fact that the average length of time from target discovery to approval of a new drug currently averages approximately 14 years, the failure rate exceeds 95%, and the cost per successful drug exceeds $2 billion, after adjusting for all of the failures."

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According to Robert J. Meyer, Director of the Virginia Center for Translational and Regulatory Sciences at the University of Virginia School of Medicine, "It is well documented that one of the major categories of expenditure in developing a new therapeutic is the expense of conducting randomized, phase 3 clinical trials, which are intended to address the regulatory expectations in the U.S. and beyond." However, Meyer doesn't think the clinical trial costs for Sovaldi are substantially higher than those for similar drugs, much less those with a list price of $84,000 for a 12-week regimen. "I think pricing is driven by what the market will bear, including the value of the drug's ability to forestall later disease," he states. "But I can't say clinical trial costs have no relationship to the price of drugs. The company must amortize those costs, especially the costs of the 50% of drugs that fail in phase 3 trials."

Gilead has declined to provide data on the cost of clinical trials for Sovaldi. On March 20, 2014, U.S. Rep. Henry Waxman (D-Calif.) and colleagues sent a letter to John Martin, PhD, Chief Executive Officer of Gilead, asking for information about the methodology Gilead used to establish Sovaldi's pricing.[1] One of the things Waxman wanted to know was "the value to the company of the expedited review provided under the priority review and breakthrough therapy designation and how any savings provided by the expedited review factored into pricing decisions for the drug." The priority review and breakthrough therapy designations are new tools that Congress has given the FDA in the past few years that enable the agency to approve a drug faster based on abbreviated clinical trials.

Cara Miller, a Gilead spokeswoman, says the company met with Waxman's staff to "share our perspective on the scientific and medical evidence for treating a disease that causes significant morbidity and mortality in the U.S. and the benefits of Sovaldi." But that perspective is not public, nor has Waxman himself published anything that Sovaldi may have shown his staff. Miller declines to discuss the costs of Sovaldi clinical trials or the relationship of those costs to Sovaldi pricing.

A Waxman spokeswoman says Gilead was "not able to answer all our questions, and [was] not able to provide us with information that adequately justified the cost of the drug."

It is not just the cost of conventional clinical trials that is at issue, but also their inclusiveness. In an interview with the *Wall Street Journal* on August 4, 2014, Arvind Goyal, MD, Medical Director of the Illinois Department of Health Care and Family Services, raised questions about the population enrolled in the Sovaldi clinical trials.[2] He complained that Gilead did not include people with alcohol and drug problems, which are prevalent among his state's Medicaid population. "If someone is using a street drug such as heroin," he said, "I can't be sure they are compliant taking Sovaldi. It is a total waste."

Miller, the Gilead spokeswoman, says: "Patients with ongoing illicit drug use such as cocaine and heroin were excluded from the clinical trials. Patients who were actively abusing alcohol were excluded from the clinical trials. However, a history of alcohol abuse or ongoing alcohol use was not exclusionary; approximately 5–10% of patients in the phase 3 studies self-reported this medical history."

Congress Looks at Possible Reforms

Because of the many structural imperfections that prevent faster, cheaper, more accurate clinical trials, Democrats and Republicans in Congress are considering what they can do to inject doses of modernity into a dusty system. The House Energy and Commerce Committee, as part of its year-long "21st Century Cures" hearings, has been exploring varieties of unconventional clinical trials—often grouped under the rubric of "adaptive" clinical trials—and looking at ways useful flexibility can be injected into FDA requirements. At hearings in July, Jay Siegel, MD, Chief Biotechnology Officer and Head of Scientific Strategy and Policy at Johnson & Johnson, said, "I believe that we now face an extraordinary opportunity to reinvent our approach to clinical trials and, as a result, to greatly increase the quality of medical care and the quality of life itself."

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The President's Council of Advisors on Science and Technology succinctly stated the problem in its 2012 report on drug innovation:[3]

> Unfortunately, there is broad agreement that our current clinical trials system is inefficient. Currently, each clinical trial to test a new drug candidate is typically organized *de novo,* requiring substantial effort, cost, and time. … Navigating all of these requirements is challenging even for large pharmaceutical companies, and can be daunting for small biotechnology firms.

U.S. Rep. Joe Pitts (R-Pa.), Chairman of the House Health Subcommittee, detailed the shortcomings of the clinical trial system when he welcomed Janet Woodcock, MD, Director of the FDA Center for Drug Evaluation and Research, to a hearing on July 11, 2014. "Widespread duplication of effort and cost also occurs because research is fragmented across hundreds of clinical research organizations, sites, and trials, and information regarding both the successes and failures of clinical trials is rarely shared among researchers," Pitts said. "It is often difficult to identify potential participants due to a shortage of centralized registries, low awareness of the opportunity to participate in clinical trials, low patient retention, and lack of engagement among community doctors and volunteers."

Dr. Woodcock said the FDA has been doing what it can to reduce clinical trial requirements, consistent with maintaining patient safety, but "some of these challenges need to be addressed by those outside of FDA." The FDA issued guidance in December 2012 on clinical trial enrichment strategies. She pointed to Novartis' Zykadia (ceritinib), a new drug for patients with a certain type of late-stage, non–small-cell lung cancer, which the FDA approved in April 2014 via a breakthrough therapy designation. "It took less than four years—versus the roughly 10 years it used to take—from the initial study of the drug to FDA approval," she stated.

The FDA granted Zykadia a conditional approval based on a phase 1, single-arm study of 163 people that investigated the maximum tolerated dose, safety, pharmacokinetics, and preliminary antitumor activity of Zykadia. Dana Cooper, a Novartis spokeswoman, declined to provide details on what the company has spent so far on clinical trials for the drug. "As we manage our research investment across a portfolio of medicine in development, we do not provide estimates of research costs for individual molecules," she says. The company is continuing phase 2 and 3 trials as a condition of FDA conditional approval. The average wholesale price for a 30-day supply of Zykadia at the recommended daily dose is $16,197, according to Red Book.

Recent FDA Efforts to Cut Approval Times

The cost of clinical trials and their required length to completion have been the subject of criticism within the pharmaceutical industry for some time. Over the past decade or so, Congress has provided the FDA with authority to approve new drugs more quickly in certain circumstances, sometimes on the basis of shortened clinical trials.[4] With Sovaldi, for example, Gilead asked for and received a priority review, which reduces the FDA review goal date from 10 to six months. The FDA also awarded Sovaldi a breakthrough therapy designation, which allows a company to submit a new drug for approval based on preliminary clinical evidence "that the drug may have substantial improvement on at least one clinically significant endpoint over available therapy." In addition, the FDA offers drug developers accelerated approval, which can be granted on the basis of studies establishing that the drug or biologic "has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

Some drugs the FDA has approved with its new authorities, based on truncated trials, have turned out to be problematic in the post-marketing period. Avandia and Avastin are two examples. "The recent history of drug misadventures provides numerous examples of rare but catastrophic side effects overlooked at current levels of testing in broader patient populations," says Thomas J. Moore, Senior Scientist at the Institute for Safe Medication Practices and Lecturer in the Department of Epidemiology and Biostatistics at The George Washington University School of Public Health and Health Services.

Moore is skeptical about the FDA's efforts to establish a new "alternative approval pathway for certain drugs intended to address unmet medical needs." Congress directed the FDA to do so in the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012,[5] the law that established the breakthrough therapy designation. The 2012 law also included language expanding the types of evidence the FDA can use to assess whether a surrogate endpoint is likely to predict clinical benefit and encouraged usage of a broader variety of endpoints for accelerated approval. Moore says the alternative approval pathway "could compromise patient safety, is unnecessary given seven existing expedited approval programs, has no clear public health justification for exposing patients to increased risks, and is insufficiently researched and documented to permit a clear evaluation."

The FDA held a hearing in February 2013 to seek input from industry and the public on the viability of a new alternative pathway. Paul Huckle, Chief Regulatory Officer for GlaxoSmithKline PLC, stated, "We believe that the proposed pathway should be considered in parallel, and in addition to, already existing regulatory pathways such as accelerated approval, fast track, priority review, and breakthrough therapy designation, and if implemented should be applied at the sponsor's request." The FDA has not published any draft, much less final, guidelines offering a new alternative pathway.

Need for More Flexibility and Infrastructure

Speeding up the FDA review process, though, is essentially nibbling around the edges of an antiquated system, where one drug is tested in a large population of people suffering from one disease, be that lung cancer, hepatitis C, or any of the conditions that afflict much smaller populations. There is broad agreement that this "one drug, one condition" methodology must change. Winds of change—actually, they are more like light breezes—are blowing through the hallways of contract

research organizations and academic medical centers, which do the majority of clinical testing. The reforms include use of biomarkers to select participants, use of "adaptive" clinical trials sponsored jointly by drug companies, and establishment of nationwide academic networks with access to electronic medical records. Study participants are chosen because they have a specific genotype that is thought to be responsive to a specific agent. Large groups of patients across numerous academic centers are recruited because those genes are found in a very small percentage of those volunteers. Often new patients are recruited on a rolling basis, under a master protocol that test sites adhere to across the country. A number of agents are tested at the same time, each one in a separate small group consisting of patients who all have the same target gene.

Lung-MAP, which is testing five lung cancer agents, is a clinical trial now getting under way that uses many of the new clinical trial techniques. It is expected to screen as many as 1,250 patients each year for more than 200 cancer-related genomic alterations. Participants will eventually be divided into five "baskets," each including patients with an identical genotype thought to be responsive to a single agent. Five agents are being tested by five companies, all of them cooperating. None of the five companies, on their own, could recruit that many patients. That kind of large population is important because each of the five biomarkers will be found in a very small percentage of people, so it is necessary to recruit large numbers in order to have enough participants in each of the five baskets.

Moving Straight From Phase 2 to Phase 3

"Another distinctive feature of Lung-MAP is the ability for a drug that is found to be effective in phase 2 to move directly into the phase 3 registration components, incorporating the patients from phase 2," explains Roy S. Herbst, MD, PhD, Ensign Professor of Medicine, Chief of Medical Oncology, and Associate Director for Translational Research at Yale Cancer Center. "This unique statistical approach can save both time and the number of patients that would be needed to program compared to conducting separate phase 2 and phase 3 studies."

As its endpoint, the trial is using "median progression-free survival," which Dr. Herbst concedes is a surrogate endpoint. He explains that any of the five agents could show a positive effect as early as the first year. But clearly nothing is certain: the efficacy of the agents, the viability of the trial's structure, or the cost savings to the five companies compared with what they would have spent had they embarked on singular, conventional trials.

Not everyone thinks the potentially fast transition from phase 2 to phase 3 is a blessing. "While this sounds attractive, this kind of adaptive trial raises many significant issues—not the least of which is the loss of the ability to conduct a true 'learn and confirm' development paradigm, which is the very heart of cogent drug development," explains the University of Virginia's Meyer. "If there is any message in the rising failure rate of phase 3 trials, I think it is that the increasingly parallel drug trials paradigm, rather than the serial learn-and-confirm model, does not allow for enough careful thought of past results to properly inform future designs."

That kind of skepticism may explain why the FDA has not opened the door very wide to adaptive studies. The agency published draft guidance in March 2010,[6] but final guidance has never appeared. Industry generally applauded the FDA's draft, but felt it was too restrictive. The draft talked about "familiar" and "less familiar" approaches, and seemed to bestow approval on the former and skepticism on the later. "The less familiar design methods incorporate methodological features with which there is little experience in drug development at this time," the draft stated.

Industry and Academia Slow to Help

To some extent, the fact that clinical trials take as long and cost as much as they do is partly the fault of the companies that conduct them, according to Meyer. He calls some of the steps in phase 3 trials "self-inflicted." A recent Tufts University study[7] showed the number of endpoints and procedures in clinical trials went up more than 60% from 2002 to 2012. At the same time, this study showed that a minority of the procedures, endpoints, and related trial costs in phase 3 trials were driven by regulatory requirements. This study estimated that non-core elements of these trials cost $4 billion to $6 billion in aggregate spending across the industry.

A significant portion of those "self-inflicted" costs come from companies reinventing the wheel every time they conduct a clinical trial. Those costs include setting up a network and developing and implementing a protocol. Some of those costs disappear when companies and academic centers avail themselves of clinical trial networks. But these networks are few and far between.

The National Institutes of Health inaugurated a Clinical and Translational Science Awards (CTSA) program in 2006.[8] It is active at 62 sites, mostly academic medical centers, and is funded at a level of nearly $500 million. The hope was for those centers to work together on specific clinical trial projects. A 2013 report from the Institute of Medicine (IOM)[9] said the program is "contributing significantly" to clinical research. But based on the number of recommendations made to improve the program, that praise seemed *pro forma.* The report described the program as being in an infant stage, with little cross-center or center-public collaboration, and hamstrung by a bureaucratic structure. It said: "The IOM committee envisions a transformation of the CTSA program from its current, loosely organized structure into a more tightly integrated network that works collectively to enhance the transit of therapeutics, diagnostics, and preventive interventions along the developmental pipeline; disseminate innovative translational research methods and best practices; and provide leadership in informatics standards and policy development to promote shared resources."

Even for a clinical trial network such as the one being developed by Lung-MAP, one can see what a huge task it is to assemble 5,000 patients, obtain and massage their personal health data, and de-identify that data. Paula Brown Stafford, MPH, President of Clinical Development at Quintiles, a major contract research organization, thinks Congress should create a central repository of accessible, securely de-identified patient-level data and make it available for research use through appropriate licensing. "And just think about the amount of time that would be cut out of the trial," she says, "from four years [for] finding patients down to 14 days because we have the

data that gives us access to identify the patients." Dr. Herbst says, for example, that Lung-MAP registered 10 patients in the first two months the trial was in progress.

No one would argue the merits of a more national clinical trial infrastructure, backed by national disease registries and fueled by electronic medical records. The use of biomarkers to select trial participants is a bit more dicey, given its reliance on diagnostic tests that may or may not have received FDA approval.

Congress is likely to include clinical trial reforms in the next reauthorization of the Prescription Drug User Fee Act (PDUFA). In past reauthorizations, the emphasis has been on speeding FDA approval, not clinical trials. Helping companies get to the FDA with a new drug application more quickly and more cheaply, in a way consistent with protecting safety and efficacy, should be the focus this time. Given the importance of this objective, it shouldn't be necessary to wait until 2017, when PDUFA is scheduled to be reauthorized for the sixth time.

REFERENCES

1. Waxman H, Pallone F, DeGette D. Letter to John Martin, PhD, Chief Executive Officer of Gilead Sciences. March 20, 2014. Available at: http://democrats.energycommerce.house.gov/sites/default/files/documents/Martin-Gilead-Sciences-Hepatitis-C-Drug-Sovaldi-Pricing-2014-3-20.pdf. Accessed August 21, 2014.
2. Silverman E. How Illinois allocates $84,000 drug for hepatitis C. *The Wall Street Journal*. August 3, 2014. Available at: http://online.wsj.com/articles/how-illinois-allocates-84-000-drug-for-hepatitis-c-1407114940. Accessed August 21, 2014.
3. President's Council of Advisors on Science and Technology. Report to the president on propelling innovation in drug discovery, development, and evaluation. September 2012. Available at: http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf. Accessed August 21, 2014.
4. Food and Drug Administration. Guidance for industry: expedited programs for serious conditions—drugs and biologics. May 2014. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf. Accessed August 21, 2014.
5. Government Printing Office. Food and Drug Administration Safety and Innovation Act of 2012. Available at: http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf. Accessed August 21, 2014.
6. Food and Drug Administration. Guidance for industry: adaptive design clinical trials for drugs and biologics. February 2010. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf. Accessed August 21, 2014.
7. Getz KA. Improving protocol design feasibility to drive drug development economics and performance. *Int J Environ Res Public Health* 2014;11(5):5069–5080. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4053871. Accessed August 21, 2014.
8. National Institutes of Health. Clinical and Translational Science Awards program. Available at: http://www.ncats.nih.gov/files/factsheet-ctsa.pdf. Accessed August 21, 2014.
9. Institute of Medicine. The CTSA Program at NIH: opportunities for advancing clinical and translational research. June 2013. Available at: http://www.iom.edu/~/media/Files/Report%20Files/2013/CTSA-Review/CTSA-Review-RB.pdf. Accessed August 21, 2014. ■